PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| *In re* Application of: | Group Art Unit: 1644 |
| KUNDIG and McCORMACK | Examiner: Phyong N. HUYNH |
| Serial No.: 09/804,464 | Docket No: 005184.00002 |
| Filed: March 13, 2001 | |

For: **MODULATION OF ALLERGIC RESPONSE**

**DECLARATION OF DR. THOMAS KÜNDIG UNDER 37 C.F.R. § 1.132**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Thomas Kündig, declare as follows:

1. I am named as an inventor of the subject matter claimed in the application referenced above.

2. I hold an M.D. degree from the University of Zürich and have worked in the fields of immunology and allergy for 14 years. My curriculum vitae is attached as Exhibit 1.

3. We conducted a clinical study that included a total of 153 human hay fever sufferers. Each of these patients was allergic to grass pollen, as assessed by skin prick testing to grass pollen extract. Patients were randomized into two study groups. Eighty-six patients in the conventional treatment group received conventional grass pollen immunotherapy. These patients were subcutaneously injected with 16 incremental doses of grass pollen extract over 20 weeks, followed by twice-weekly subcutaneous injections of a maintenance dose corresponding to 100

μg alum-absorbed grass pollen extract (100,000 so called "SQ-E units"). Sixty-seven patients in the intralymphatic group received three injections of 1 μg of the same alum-absorbed grass pollen extract into a superficial subcutaneous lymph node of the groin spaced four weeks apart. The efficacy of both the conventional and the intralymphatic treatments were assessed four months after the initial treatment. The protocol is shown in Exhibit 2.

4. To assess efficacy, patients in both treatment groups were evaluated for their sensitivity to the allergen by nasal provocation with an extract of the same pollen extract. Fifty μl of pollen extract were administered under rhinoscopic control onto the mucosa of the lower concha. A first dose of 100 SQ-E (approximately 0.1 μg of grass pollen extract) was followed after 30 minutes by 1,000 SQ-E (approximately 1 μg), then by 10,000 SQ-E (approximately 10 μg) and finally by 100,000 SQ-E (approximately 100 μg) after 60 and 90 minutes, respectively. The following symptoms and scores were recorded: ocular or nasal itching (0 = none; 1 = mild, *i.e.*, slight sensation; 2 = moderate, *i.e.*, definite sensation; and 3 = severe, *i.e.*, need to rub nose or eyes); runny nose (0= none; 1 = mild, *i.e.*, slight sensation; 2= moderate, *i.e.*, definite sensation; and 3 = severe, *i.e.*, need to blow or wipe nose); nasal congestion (0= none; 1= mild, *i.e.*, slight sensation; 2 = moderate, *i.e.*, definite sensation; and 3= severe, difficult to breathe through one or both nares); and sneezing (0= none; 1= mild, *i.e.*, 1-2 sneezes; 2 = moderate, *i.e.*, 3-4 sneezes; and 3= severe, *i.e.*, 5 or more sneezes). The results are shown in Exhibit 3.

5. The upper left panel of Exhibit 3 depicts the symptom scores observed after nasal provocation with 100 SQ-E units (approx. 0.1 μg of pollen extract). At this low pollen concentration the intranodal group shows fewer symptoms after treatment, but due to the generally low symptom scores at this low pollen concentration, the latter improvement of the intranodal group shows no statistical significance (p= 0.45). The upper right panel of Exhibit 3

shows the symptom scores after nasal provocation with 1,000 SQ-E units (approximately 1 μg of pollen extract). Again the intranodal group of patients shows a lower symptom score after treatment, but again the overall symptom scores are low, so that the improvement is not statistically significant (p=0.07).

6. The lower left panel of Exhibit 3 shows the symptom scores after nasal provocation with 10,000 SQ-E units (approximately 10 μg of pollen extract). Because of the higher pollen concentration, the overall symptom scores are higher and the improvement of the intranodal group becomes statistically significant (average score before treatment 4.47, compared with 1.9 after treatment). The lower right panel of Exhibit 3 shows the symptom scores after nasal provocation with 100,000 SQ-E grass pollen extract (approximately 100 μg pollen extract). Before treatment the intranodal group showed an average symptom score of 9.63; after treatment, the symptom score is reduced to 5.05. This change is statistically highly significant (p=0.002).

7. Thus, intralymphatic administration of allergen administration is more efficient than subcutaneous administration of the same allergen. No more than three intranodal injections of an allergen are sufficient to desensitize human patients to the allergen, as assessed by sensitivity to the allergen. This permits a reduced number of injections and therefore substantially shortens the duration of treatment.

8. Patients that were desensitized by only 3 intranodal injections were assessed by nasal provocations tests 4 months after the beginning of treatment. As shown in Exhibit 4, this patient group tolerated approximately 10 times higher pollen concentrations after treatment. In contrast, subcutaneously desensitized patients showed no significant improvement of their nasal provocation thresholds. In order to achieve a 10-fold increase in the nasal provocation threshold

conventional subcutaneous immunotherapy usually has to be continued for 3 years, as demonstrated by Wihl *et al.* for tree pollen (*Allergy 43*, 363-69, 1988; Exhibit 6). Similarly, Pegelow *et al.* (*Allergy 39*, 275-90, 1984; Exhibit 7) showed that after 3 years of immunotherapy with grass pollen the average increase in the nasal provocation threshold is not more than a factor of 10.

9. It is unexpected that treatment with merely three injections of 1 μg more efficiently reduces the symptom score than the extensive conventional subcutaneous regimen with 20 incremental injections up to 100 μg of the same pollen extract. Based on these results, I would expect that the efficiency of desensitization with other allergens such as venoms, animal dander, and dust mite would be similarly enhanced by intranodal administration.

10. Pollen-specific IgG also was measured before treatment and four months after the beginning of treatment. No significant changes were observed. Amongst all IgG subclasses, subclass IgG4, if at all, is the one subclass where increases have been reported by other groups. The graph shown in Exhibit 5 depicts specific IgG4 against the major allergenic grass in Europe (*i.e., Phleum pratensae*) in patients treated by intralymphatic allergen injections. IgG4 titers were measured by the Pharmacia CAP™ method, which permits a quantitative assessment. There was no significant titer change in *Phleum pratensae*-specific IgG4 before and after treatment. Thus, the mechanism of intralymphatic desensitization does not depend on induction of allergen-specific IgG4 antibodies.

11. A total of 20 systemic allergic adverse events were observed during a one hour post-injection wait for the conventional group. Two of these events (asthma attacks) were classified as severe (grade 3 according to H.L. Müller, *New Engl. J. Med. 261*, 374-77, 1959; J. *Asthma Res. 3*, 331-33, 1966). Eighteen of thes events were classified as mild or moderate

or angioedema. In contrast, only six systemic allergic events were observed during a two hour post-injection wait for the intralymphatic group. These patients suffered from flush, urticaria or angioedema (grades 1 and 2 according to H.L. Müller). This demonstrates that the frequency and severity of adverse events are reduced with intralymphatic treatment compared to conventional treatment.

12. At the one year follow up visit, 40 of the original 86 patients in the conventional treatment group had dropped out of the study. In contrast, only three of the original 67 patients in the intralymphatic treatment group had dropped out. Thus, patients receiving intralymphatic treatment show better compliance and are more likely to finish their treatment.

13. I declare that all statements made herein of my own knowledge are true and that I believe all statements made on information and belief are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Date Thomas Kündig, M.D.

EXHIBIT 1

**Curriculum vitae of Thomas Kündig**


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|---|---|
| Name: | Kündig |
| First Name, Middle Name: | Thomas, Martin |
| Titels: | PD Dr.med. |
| Birth data: | 22.1.1963 |
| Nationality: | Schwitzerland and USA |
| Working place: | Dermatologische Klinik<br>Gloriastr. 31<br>8091 Zürich<br>Tel: 0041-1-255-3973<br>FAX: 0041-1-255-4418 |


**Achievements:**

1981 Graduation
Mathemathical-Scientific type (Typus C),
Kantonsschule Zürcher Oberland

1987 MD degree
University of Zürich

1988 Medical Thesis
in respiratory physiology, supervisor Prof. E.A. Koller
University of Zürich

1988 Educational Commission for Foreign Medical Graduates
Basic Sciences, Clinical Sciences and English
Bern

1991 Post-graduate Course in Experimental Medicine
especially Immunology, supervisor Prof. R.M. Zinkernagel
Universität Zürich

1998 Venia legendi in Experimental Immunology and Experimental Dermatology

**Working Places:**

| | | | |
|---|---|---|---|
| Kreisspital Wetzikon<br>Dr. R. Stahel | Resident | 1988-89 | Surgery |
| Inst. for Experimental Immunology<br>Universität Zürich<br>Prof. R.M. Zinkernagel | Post-doc | 1989-92 | Immunology |
| Dept. of Medical Biophysics<br>University of Toronto<br>Prof. T.W.Mak | Post-doc | 1992-95 | Immunology |
| Dermatologische Klinik<br>Universität Zürich<br>Prof. G. Burg | Oberassistent<br>Oberarzt | 1995-99<br>1999- | Dermatology |

**Awards and Honors:**

Award for best Marks at Graduation Exams 1987
Fellowship for Post-graduate Course in Experimental Medicine 1989-91.
Fellowship as an advanced researcher by Swiss National Science Foundation 1992-94.
Venia legendi in Experimental Immunology and Experimental Dermatology 1998
Georg-Friedrich Götz Award by the University of Zürich 1999 for outstanding medical research on the development of a new method to enhance the immunogenicity of vaccines
Affiliated Researcher of the Ludwig Institute for Cancer Research

## Publications (Original):

Boutellier, U. , **T. M. Kündig,** and E. A. Koller
Delay variations in automatic respiratory analysis systems.
*Pflügers Archiv* (1986) 234:6.

Boutellier, U. , **T. M. Kündig,** U. Gomez, P. Pietsch, and E. A. Koller. 1987. Respiratory phase detection and delay determination for breath-by-breath analysis.
*J. Appl. Physiol.* (1987) 62:837.

Binder, D. and **T. M. Kündig**
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Althage, A. , B. Odermatt, D. Moskophidis, **T. Kündig,** H. Hengartner, and R. M. Zinkernagel
Immunosuppression by lymphocytic choriomeningitis virus infection: competent effector T and B cells but impaired antigen presentation.
*Eur. J. Immunol.* (1992) 22:1803.

**Kündig, T.** , A. Althage, H. Hengartner, and R. M. Zinkernagel
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*Proc. Natl. Acad. Sci. USA* (1992) 89:7757.

**Kündig, T. M.**, H. Hengartner, and R. M. Zinkernagel
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Oehen, S. , H. P. Waldner, **T. M. Kündig**, H. Hengartner, and R. M. Zinkernagel
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*J. Exp. Med.* (1993) 176:1273.

Castelmur, I. , C. DiPaolo, M. F. Bachmann, H. Hengartner, R. M. Zinkernagel, **T. M. Kündig**
Comparison of the sensitivity of in vivo and in vitro assays for detection of antiviral cytotoxic T cell activity.
*Cell. Immunol.* (1993) 151:460.

**Kündig, T. M.**, H. Schorle, M. F. Bachmann, H. Hengartner, R. M. Zinkernagel, and I. Horak.
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Shahinian, A. , K. Pfeffer, K. P. Lee, **T. M. Kündig**, K. Kishihara, A. Wakeham, K. Kawai, P. S. Ohashi, C. B. Thompson, and T. W. Mak
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Formalin inactivation of vesicular stomatitis virus impairs T-cell but not T-help-independent B-cell responses
*J. Virol.* (1993) 67:3917.

**Kündig, T. M.**, I. Castelmur, M. F. Bachmann, D. Abraham, D. Binder, H. Hengartner, and R. M. Zinkernagel
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*J. Virol.* (1993) 67:3680.

Pfeffer, K. , T. Matsuyama, **T. M. Kündig**, A. Wakeham, K. Kishihara, A. Shahinian, K. Wiegmann, P. S. Ohashi, M. Krönke, and T. W. Mak
Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to L. monocytogenes infection.
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*J. Immunol.* (1993) 151:699.

**Kündig, T. M.**, M. F. Bachmann, L. Lefrancois, L. Puddington, H. Hengartner, and R. M. Zinkernagel
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Matsuyama, T. , T. Kimura, M. Kitagawa, K. Pfeffer, T. Kawamaki, N. Watanabe, **T. M. Kündig**, R. Amakawa, K. Kishihara, A. Wakeham, J. Potter, K. Furlonger, A. Narendran, H. Suzuki, P. S. Ohashi, C. J. Paige, T. Taniguchi, and T. W. Mak. Targeted disruption of IRF-1 or IRF-2 results in abnormal type I IFN gene induction and aberrant lymphocyte development.
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*Science* (1993) 262:1448.

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**Kündig, T. M.**, M. F. Bachmann, S. Oehen, U. W. Hoffmann, J. L. Simard, C. P. Kalberer, H. Pircher, P. S. Ohashi, H. Hengartner, and R. M. Zinkernagel
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**Kündig, T. M.**, A. Shahinian, K. Kawai, H. W. Mittrücker, E. Sebzda, T. W. Mak, and P. Ohashi
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*J. Exp. Med.* (1996) 183:1415.

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*J. Exp. Med.* (1996) 183:2481.

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*J. Exp. Med.* (1996) 183:1093.

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Dommann-SN; Dommann-Scherrer-CC; Ziegler-T; Meyer-J; Trueb-RM; **Kundig-T**; Panizzon-R; Burg-G
Expression of intercellular adhesion molecule 3 (CDw50) on endothelial cells in cutaneous lymphomas. A comparative study between nodal and cutaneous lymphomas.
*Am-J-Dermatopathol.* 1997 Aug; 19(4): 391-5

**Kündig-TM**; Trueb-RM; Krasovec-M.
Lupus profundus/panniculitis
*Dermatology.* 1997; 195(1): 99-101

Zinkernagel-RM; Ehl-S; Aichele-P; Oehen-S; **Kundig-T**; Hengartner-H
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Krause-MH; Torricelli-R; **Kundig-T**; Trueb-RM; Hafner-J
[Dapsone in granulomatous rosacea]
*Hautarzt.* 1997 Apr; 48(4): 246-8

Wallace-VA; Penninger-JM; Kishihara-K; Timms-E; Shahinian-A; Pircher-H; **Kundig-TM**; Ohashi-PS; Mak-TW
Alterations in the level of CD45 surface expression affect the outcome of thymic selection.
*J-Immunol.* 1997 Apr 1; 158(7): 3205-14

Kozieradzki-I; **Kundig-T**; Kishihara-K; Ong-CJ; Chiu-D; Wallace-VA; Kawai-K; Timms-E; Ionescu-J; Ohashi-P; Marth-JD; Mak-TW; Penninger-JM
T cell development in mice expressing splice variants of the protein tyrosine phosphatase CD45.
*J-Immunol.* 1997 Apr 1; 158(7): 3130-9

Bachmann-MF; **Kundig-TM**; Hengartner-H; Zinkernagel-RM
Protection against immunopathological consequences of a viral infection by activated but not resting cytotoxic T cells: T cell memory without "memory T cells"?
*Proc-Natl-Acad-Sci-U-S-A.* 1997 Jan 21; 94(2): 640-5

Bachmann-MF; **Kundig-TM**; Speiser-DE; McKall-Faienza-K; Kishara-K; Mak-TW; Ohashi-PS
T-cell-independent antiviral B cell responses in CD45-deficient mice.
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CD44 regulates hematopoietic progenitor distribution, granuloma formation, and tumorigenicity.
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Expression of intercellular adhesion molecule 3 (CDw50) on endothelial cells in cutaneous lymphomas. A comparative study between nodal and cutaneous lymphomas.
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Lupus profundus/panniculitis
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*J Invest Dermatol* 117:000-000, 2001

Urtikaria und Quincke-Oedem
**T.M. Kündig**
*Allergolist* 2001

Therapie der chronischen Urtikaria und der rezidivierenden Quincke-Oedeme
**T.M. Kündig**
*Therapeutische Umschau*, Band 58, Heft 5, 2001, Seite 321-324

Verfahren zur Steigerung der Immunogenität von Impfstoffen
**T.M. Kündig**
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